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Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE)

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Background: Interleukin (IL)-13 plays a key role in type 2 inflammation and is an emerging pathogenic mediator in atopic dermatitis (AD).

Objective: We investigated the efficacy and safety of lebrikizumab, an IL-13 monoclonal antibody, as an add-on to topical corticosteroid (TCS) treatment.

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Conflicts of interest: Dr Simpson reports grants, personal fees, and nonfinancial support from Roche-Genentech during the conduct of the study; personal fees from AbbVie, Celgene, Dermira, Galderma, LEO Pharma, Menlo Therapeutics, Sanofi Genzyme, and Valeant Pharmaceutical; grants and personal fees from Anacor Pharma, GlaxoSmithKline, and Regeneron Pharmaceuticals; grants from MedImmune, Novartis, Roivant Sciences, Tioga Pharmaceuticals, and Vanda Pharmaceuticals; and grants and personal fees from Eli Lilly outside the submitted work. Dr Flohr reports personal fees from Sanofi Regeneron outside the submitted work. The views expressed are those of the author(s), and not necessarily those of the UK NIHR or the UK Department of Health. Dr Eichenfield reports personal fees and nonfinancial support from Roche-Genentech during the conduction of the study and the following activities: Sanofi Regeneron (investigator, consultant, speaker); Cutanea (consultant); Dermavant (investigator); Eli Lilly (consultant); Galderma (investigator, consultant); Anacor/Pfizer (investigator, consultant); Novartis (consultant); LEO (investigator, consultant); Medimetriks (consultant); and Valeant (investigator, consultant). Dr Bieber has the following declaration of interests: Roche (consultant); Sanofi Regeneron (investigator, consultant, speaker); Eli Lilly (investigator, consultant, speaker); Galderma (investigator, consultant); Pfizer (investigator, consultant); Novartis (investigator, consultant); GlaxoSmithKline (consultant, speaker); LEO (investigator, consultant, speaker); and AbbVie (consultant). Dr Sofen reports personal fees from Genentech during the conduction of the study and personal fees from Regeneron and LEO outside the submitted work. Dr Taïeb has nothing to disclose. Drs Owen, Putnam, DeBusk, Lin, and Omachi are employees of Genentech, a member of the Roche group, and have a patent pending. Dr Yen is an employee of Roche and has a patent pending. Dr Voulgari is an employee of Roche Products Ltd.

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Methods: A randomized, placebo-controlled, double-blind, phase 2 study. Adults with moderate-to-severe AD were required to use TCS twice daily and then randomized (1:1:1:1) to lebrikizumab 125 mg single dose, lebrikizumab 250 mg single dose, lebrikizumab 125 mg every 4 weeks for 12 weeks, or placebo every 4 weeks for 12 weeks, after a 2-week TCS run-in. The primary endpoint was percentage of patients achieving Eczema Area and Severity Index (EASI)-50 at week 12.

Results: In total, 209 patients received the study drug. At week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg every 4 weeks (82.4%; $P = .026$) than placebo every 4 weeks (62.3%); patients receiving a single dose of lebrikizumab showed no statistically significant improvements in EASI-50 compared with placebo. Adverse events were similar between groups (66.7% all lebrikizumab vs 66.0% placebo) and mostly mild or moderate.

Limitations: Protocol-mandated twice daily TCS treatment limits our understanding of the efficacy of lebrikizumab as a monotherapy. The short study duration did not enable long-term efficacy or safety evaluations.

Conclusion: When combined with TCS, lebrikizumab 125 mg taken every 4 weeks led to a significant improvement and was well tolerated in patients with moderate-to-severe AD. (J Am Acad Dermatol 2018;78:863-71.)

Key words: anti-IL-13; atopic dermatitis; EASI; lebrikizumab; pruritus; topical corticosteroids.

CAPSULE SUMMARY

- Interleukin 13 (IL-13) is overexpressed in patients with atopic dermatitis (AD).
- Lebrikizumab, a monoclonal antibody against IL-13, was superior to placebo in patients with AD when administered subcutaneously every 4 weeks along with topical corticosteroids.
- IL-13 inhibition with lebrikizumab could reduce the need for oral immunosuppressive therapy for patients with AD.

Atopic dermatitis (AD) is a chronic skin disorder characterized by intensely pruritic, eczematous lesions accompanied by a disrupted skin barrier and type 2 inflammation.[1] AD is one of the most common dermatologic diagnoses worldwide and its burden is multidimensional, impacting sleep, psychosocial activities, and health-related quality of life.[2-4] In moderate-to-severe AD, potent topical corticosteroids (TCS), calcineurin inhibitors, phototherapy, and conventional immunosuppressive medications (eg, cyclosporine) are often required. However, efficacy of topical therapies can be limited, and their frequent use is cumbersome and carries the risk for side effects.[5] Standard systemic treatments used for moderate-to-severe disease also carry significant risks.[6]

Interleukin (IL)-13 plays a central role in type 2 inflammation, and certain gene polymorphisms are associated with increased risk for AD.[7] There is increased expression of IL-13 mRNA in skin biopsy specimens from patients with AD relative to healthy controls, and levels of IL-13 mRNA expression correlate with AD disease severity.[8,9] Furthermore, overexpression of IL-13 has been shown to reduce epithelial integrity via the down-regulation of key skin barrier components.[10,11] Treatment of AD with systemic agents such as cyclosporine can decrease skin IL-13 levels,[12] and recent trials have reported improved clinical responses in patients with moderate-to-severe AD treated with dupilumab, a monoclonal antibody against IL-4Rα, which inhibits IL-13/IL-4 signaling.[13,14] Together, these data support IL-13 as a key mediator in AD.

In theory, targeting the most central pathologic mediators in AD might maximize efficacy and limit toxicity. Lebrikizumab is a monoclonal antibody that binds specifically to soluble IL-13 with high affinity, preventing IL-13Rα1/IL-4Rα heterodimerization and subsequent signaling.[15,16] Lebrikizumab has previously been investigated for the treatment of asthma, and data have accumulated from 11 randomized clinical trials involving 4411 individuals.[15,17-20] After promising phase 2b data in uncontrolled asthma, only 1 of the 2 phase 3 studies in severe adult asthma showed a statistically significant reduction in asthma exacerbations in the primary analysis population. Nonetheless, based on IL-13's involvement in multiple pathways important to AD pathogenesis, lebrikizumab represents a novel targeted therapy in AD.

Abbreviations used:

AD:	atopic dermatitis
ADIQ:	Atopic Dermatitis Impact Questionnaire
AE:	adverse event
BSA:	body surface area
EASI:	Eczema Area and Severity Index
IGA:	Investigator Global Assessment
IL-4:	interleukin-4
IL-13:	interleukin-13
SCORAD:	SCORing Atopic Dermatitis
TCS:	topical corticosteroids
VAS:	Visual Analog Scale

In this proof-of-concept phase 2 study, we investigated the efficacy and safety of lebrikizumab, compared with placebo, as an add-on therapy to TCS in adults with moderate-to-severe AD.

METHODS

Study design

TREBLE was a randomized, placebo-controlled, double-blind, phase 2 study conducted at 62 centers. It included a 2-week TCS run-in period before the 12-week treatment period. Patients were instructed with daily e-Diary reminders to apply medium-potency TCS (0.1% triamcinolone acetonide) to all lesional skin during run-in and study treatment. For lesions affecting the face or intertriginous areas, 2.5% hydrocortisone could be used. TCS was included in the regimen because, historically, studies on biologic therapies in a monotherapy setting have led to high dropout/imputed patient failure rates, in particular because of disease severity. In addition, add-on TCS treatment reflects real-life clinical practice in patients with moderate-to-severe AD. Further details about study design, pharmacokinetics, outcome measures, and statistical analyses are provided in the online Supplementary Appendix (available at http://www.jaad.org). The study was undertaken in accordance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki. All study documents and procedures were approved by the appropriate institutional review boards and ethics committees at each study site and each patient provided written informed consent before study participation. An internal monitoring committee was incorporated to monitor patient safety throughout the study.

Patients

Eligible patients were aged 18-75 years and had a diagnosis of moderate-to-severe AD with an inadequate response to TCS (≥1-month history within 3 months before screening) and regular emollient. Other key inclusion criteria were Eczema Area and Severity Index (EASI) ≥14 and Investigator Global Assessment (IGA) score ≥3 at screening and end of the run-in period and AD involvement of ≥10% of body surface area (BSA) and Pruritus Visual Analog Scale (VAS) score ≥3 (measured as part of SCORing Atopic Dermatitis [SCORAD]) at screening.

Exclusion criteria included use of topical calcineurin inhibitors; recent systemic immunosuppressive therapies or phototherapy; and evidence of other skin conditions, including T-cell lymphoma or allergic contact dermatitis.

Randomization

Patients were randomized 1:1:1:1 to receive lebrikizumab 125 mg single dose at baseline, 250 mg single dose at baseline, 125 mg once every 4 weeks, or placebo every 4 weeks for 12 weeks.

Procedures

The 12-week treatment period was followed by an 8-week safety follow-up period, during which patients could apply TCS as needed. Disease severity assessments included EASI, IGA, and SCORAD; patient-reported outcome data were collected by using the Dermatology Life Quality Index and AD Impact Questionnaire (ADIQ).[21]

Outcomes

The primary endpoint was the percentage of patients achieving a 50% reduction in EASI score from baseline (EASI-50) at week 12. This EASI-50 also equates to a minimum of a 7-point improvement from the required baseline score ≥14 in this study, which is above the minimum clinically important difference of 6.6 points.[22] Key secondary endpoints included the percentages of patients achieving EASI-75, IGA score of 0 or 1, and SCORAD-50 at week 12. Safety outcomes, including treatment-emergent adverse events (AEs) and serious AEs, were monitored at each visit from baseline to week 20. Eosinophil-associated AEs were also monitored.

Statistical analyses

Primary and secondary efficacy analyses included all patients who were randomized and received ≥1 dose of study drug and were analyzed according to the treatment assigned at randomization. Safety analyses included all patients who received ≥1 dose of study drug and were analyzed according to the treatment received. The Cochran-Mantel–Haenszel χ^2 test was used to compare the proportions of patients with EASI-50 at week 12 in each of the lebrikizumab groups versus placebo, stratified by randomization stratification factor

Table I. Baseline characteristics and demographics of patients with atopic dermatitis included in study

Characteristic	Lebrikizumab 125 mg single dose, n = 52	Lebrikizumab 250 mg single dose, n = 53	Lebrikizumab 125 mg Q4W, n = 51	Placebo, n = 53
Mean age, y (SDv)	34.9 (12.7)	34.4 (12.3)	36.6 (12.3)	38.7 (13.2)
Male, n (%)	34 (65.4)	31 (58.5)	35 (68.6)	36 (67.9)
Race, n (%)				
White	36 (69)	43 (81)	36 (71)	35 (66)
Asian	13 (25)	9 (17)	15 (29)	16 (30)
Other	3 (6)	1 (2)	0	2 (4)
Mean Rajka-Langeland (SDv)	8.50 (0.73)	8.49 (0.67)	8.34 (0.87)	7.96 (1.06)
Mean EASI (SDv)	24.6 (11.1)	26.3 (12.2)	26.9 (11.7)	23.6 (9.2)
Mean SCORAD (SDv)	56.5 (13.4)	58.9 (13.5)	60.8 (13.6)	59.2 (12.0)
Mean IGA (SDv)	3.2 (0.4)	3.3 (0.5)	3.2 (0.42)	3.2 (0.4)
IGA = 4, n (%)	10 (19)	15 (28)	11 (22)	11 (21)
Mean % BSA affected (SDv)	44.2 (21.3)	50.5 (24.7)	48.5 (22.7)	43.4 (22.0)

BSA, Body surface area; *EASI*, Eczema Area Severity Index; *IGA*, Investigator Global Assessment; *Q4W*, every 4 weeks; *SCORAD*, SCORing Atopic Dermatitis; *SDv*, standard deviation.

geographic region (United States and Canada, Europe, and other). Patients missing an EASI score at week 12 were considered nonresponders.

RESULTS

Trial patients

Overall, 209 patients received study drug (n = 53 placebo; n = 156 lebrikizumab) (Supplemental Fig 1; available at http://www.jaad.org). Baseline characteristics of patients were similar across treatment groups (Table I). There was a high compliance rate of TCS use among all treatment groups, with TCS used on average from baseline to week 12 on 86.8% of days for patients taking the 125-mg single dose, 86.7% of days for patients taking the 250-mg single dose, 91.9% of days for patients taking the 125-mg dose every 4 weeks, and 88.2% of days for patients taking placebo. Further details of the results are provided in the online Supplementary Appendix.

Primary outcome

At week 12, significantly more patients in the lebrikizumab 125 mg every 4 weeks group achieved EASI-50 compared with placebo (82.4% vs 62.3%; P = .026) (Fig 1, *A*). However, the response in the lebrikizumab single dose groups was not statistically significant at week 12. In the every 4 weeks arm, the response curve showed an upward sloping trajectory in the final weeks of treatment (Fig 2, *A*). Notably, patients in the placebo group, with protocol-mandated twice daily TCS application, showed a high response rate, with 62.3% of patients exhibiting an EASI-50 response at week 12.

Other AD severity measures

The proportion of patients achieving an EASI-75 response at week 12 was significantly greater in the 125 mg every 4 weeks group (54.9%; P = .036) compared with placebo (34.0%) but did not achieve statistical significance in the 125 mg and 250 mg single dose groups (Fig 1, *B*). As with the EASI-50 response, patients in the 125 mg every 4 weeks group showed continued improvement in EASI-75 over the final weeks of the treatment period (Fig 2, *B*).

The percentage of patients who achieved an IGA of 0 or 1 at week 12 was higher in all lebrikizumab groups compared with placebo (Fig 1, *C*; Fig 2, *C*), but while there was a trend toward statistical significance with the 125 mg every 4 weeks group compared with placebo (33.3% vs 18.9%; P = .098), single doses did not achieve statistical significance (Supplemental Table I; available at http://www.jaad.org).

SCORAD-50 at week 12 was achieved by more patients in the lebrikizumab 125 mg every 4 weeks group (51.0%; P = .012) and 250 mg single dose group (47.2%; P = .030) than the placebo group (26.4%) (Fig 1, *D*; Fig 2, *D*). The greatest reduction in BSA affected at week 12 was observed in the lebrikizumab 125 mg every 4 weeks group (57.7% reduction). Because there were also improvements in BSA affected in the placebo group (47.4%), placebo-corrected efficacy for BSA was not statistically significant (P = .38).

Patient-reported symptoms and quality of life

There were adjusted mean percent reductions from baseline pruritus VAS of 34.9%, 32.8%, and 40.7% in the lebrikizumab 125 mg single dose, 250 mg single dose, and 125 mg every 4 weeks groups, respectively (Fig 3, *A*). The placebo group also showed reductions from baseline pruritus VAS (27.5%), which resulted in the placebo-corrected efficacy not being statistically significant (P = .40

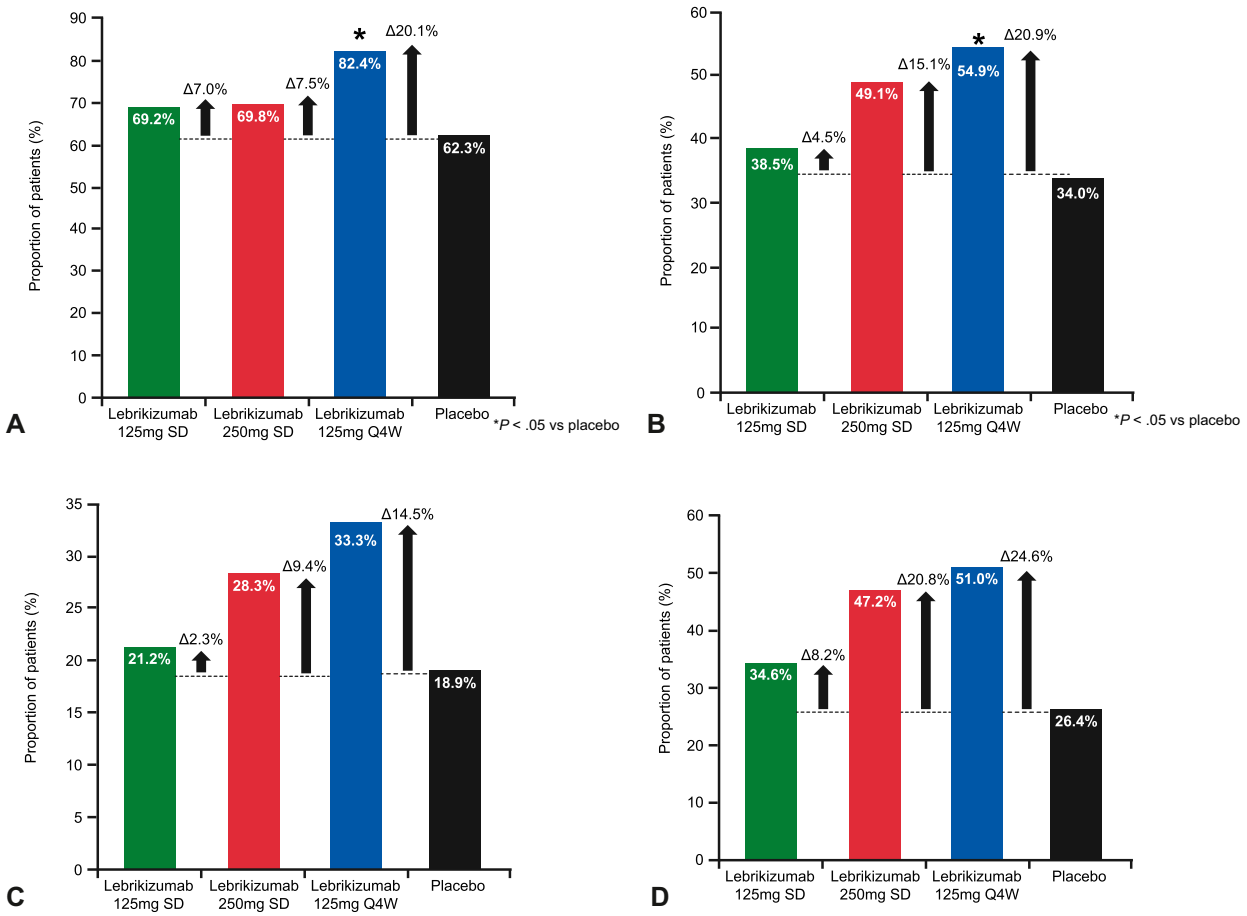

Fig 1. Proportion of atopic dermatitis patients achieving (**A**) a 50% reduction of Eczema Area and Severity Index, (**B**) a 75% reduction of Eczema Area and Severity Index, (**C**) an Investigator Global Assessment of 0 or 1, and (**D**) a 50% reduction of SCORing Atopic Dermatitis at week 12 of lebrikizumab treatment. *Q4W*, Every 4 weeks; *SD*, single dose.

[125 mg single dose], $P = .54$ [250 mg single dose], and $P = .13$ [125 mg every 4 weeks]) (Supplemental Table I; available at http://www.jaad.org). Improvements in pruritus VAS during the 2-week TCS run-in were quantitatively larger, in percentage terms, than improvements in overall disease severity measures (Supplemental Table II).

There were also improvements in sleep loss VAS, with higher mean reductions from baseline in the lebrikizumab 125 mg single dose (53.1%; $P = .029$), 250 mg single dose (47.2%; $P = .076$), and 125 mg every 4 weeks (53.6%; $P = .023$) groups than in the placebo group (22.6%) (Fig 3, *B*; Supplemental Table I).

Lebrikizumab groups showed numerical improvements, relative to placebo, in ADIQ and Dermatology Life Quality Index scores from baseline to week 12, with ADIQ showing borderline statistical significance for the 125 mg every 4 weeks group ($P = .057$), but results were otherwise not statistically significant (Fig 3, *C* and *D*; Supplemental Table I).

Safety

Lebrikizumab was well tolerated, and there were no imbalances in proportions of patients reporting AEs, serious AEs, events leading to discontinuation, and overall infections when comparing all lebrikizumab-treated patients with placebo (Supplemental Table III; available at http://www.jaad.org). There were no dose-response relationships in adverse events. Three (2%) patients in the lebrikizumab group (all doses combined) and 1 (2%) patient in the placebo group experienced an AE that led to withdrawal from study. There were no deaths, anaphylactic reactions, malignancies, or protocol-defined parasitic or targeted intracellular infections of interest. Injection site reactions occurred infrequently (1.3% all lebrikizumab groups and 1.9% placebo group); all events were nonserious and lasted a median of 1-3 days.

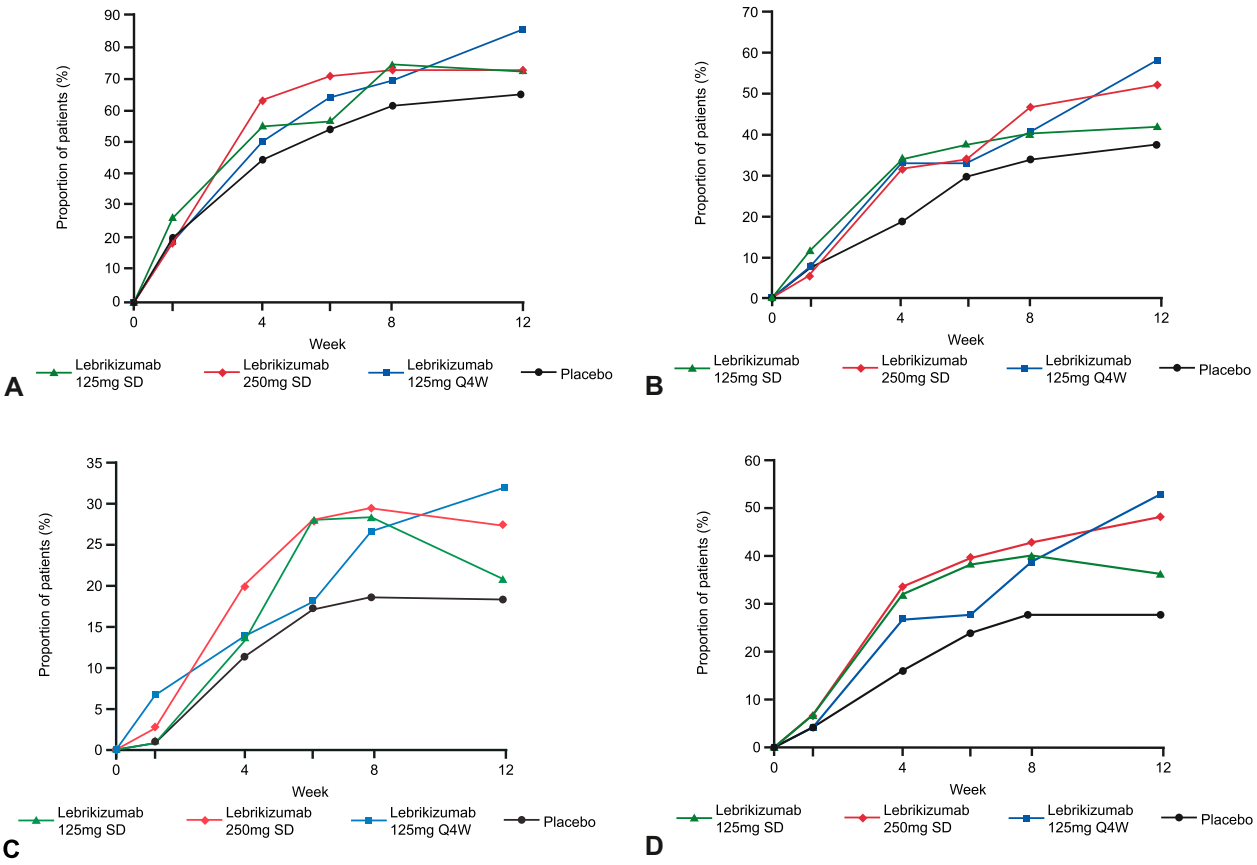

Fig 2. Proportion of atopic dermatitis patients receiving lebrikizumab achieving (**A**) a 50% reduction of Eczema Area and Severity Index, (**B**) a 75% reduction of Eczema Area and Severity Index, (**C**) an Investigator Global Assessment of 0 or 1, and (**D**) a 50% reduction of SCORing Atopic Dermatitis over time. *Q4W*, Every 4 weeks; *SD*, single dose.

DISCUSSION

Lebrikizumab provided a treatment benefit on top of rigorous TCS therapy in patients with moderate-to-severe AD who had an inadequate response to TCS. The study met its primary endpoint, with a statistically greater proportion of patients in the lebrikizumab 125 mg every 4 weeks group achieving an EASI-50 response compared with placebo. The upward sloping response curves over the final weeks of the treatment period suggest that the response plateau might not have been reached by week 12 for lebrikizumab 125 mg every 4 weeks, and that a longer treatment duration might lead to improved efficacy. Although improvements with the single doses were not statistically significant at week 12, the significant responses observed with the highest lebrikizumab dose (125 mg every 4 weeks) might indicate a dose-response relationship.

Dosing within this study was based largely on experience from the lebrikizumab asthma program and the objective of characterizing both dose-response relationships and dosing frequency requirements in AD. The dose-response relationships observed across multiple endpoints and the trends toward improved efficacy with increasing dose and duration suggest that further increases in the dose or treatment duration could improve efficacy. Notably, the lebrikizumab 250 mg single dose group showed numerically higher responses at earlier time points for several outcomes, suggesting the potential benefit of either higher dosing (eg, 250 mg every 4 weeks) or a loading dose. The observed differences in the lebrikizumab dose-response relationship between forced expiratory volume in 1 second in asthma patients[17] and EASI and IGA endpoints in AD patients suggest that AD might require higher doses of lebrikizumab to achieve a response plateau. This would suggest a higher IL-13 burden in AD than in asthma. Further studies in AD will be required to confirm whether additional clinical benefit can be observed with tailored dosing.

Lebrikizumab was generally well tolerated, and AE rates were similar between treatment groups.

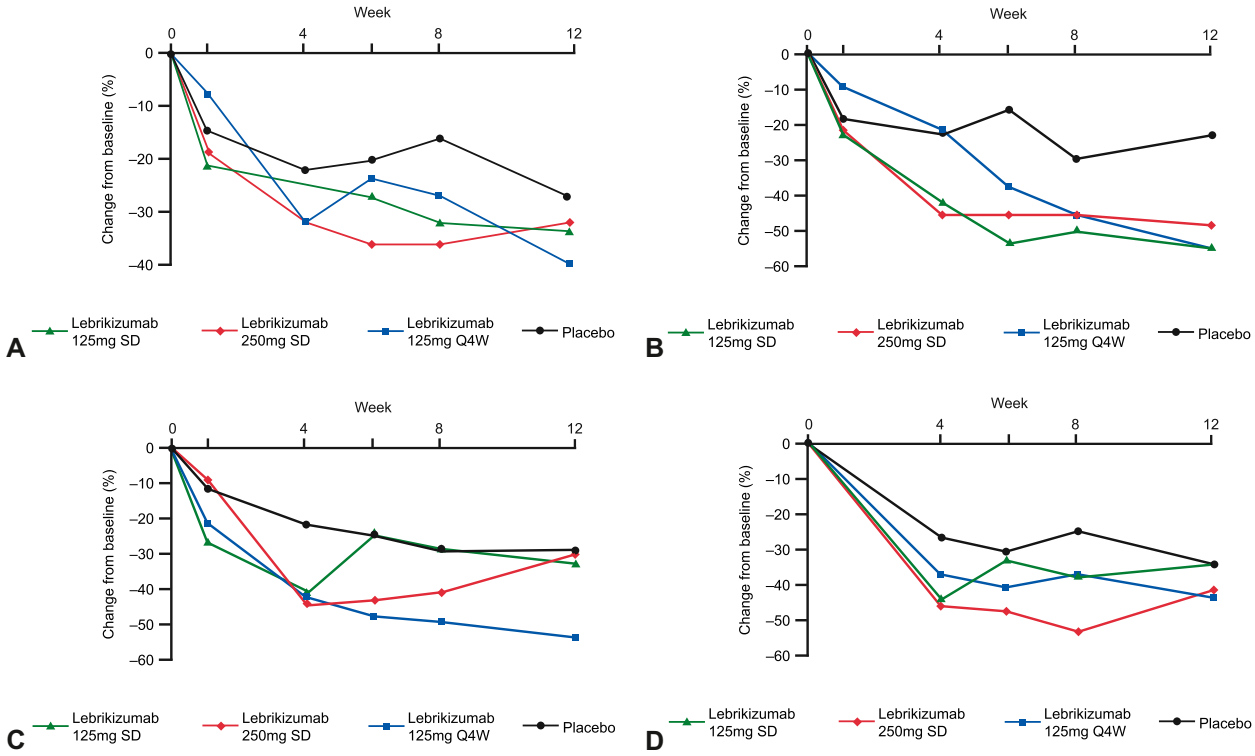

Fig 3. Adjusted mean percent change from baseline in (**A**) pruritus Visual Analog Scale, (**B**) sleep loss Visual Analog Scale, (**C**) Atopic Dermatitis Impact Questionnaire, and (**D**) Dermatology Life Quality Index over time in atopic dermatitis patients receiving lebrikizumab. *Q4W*, Every 4 weeks; *SD*, single dose.

This safety profile is consistent with that observed in the extensive asthma program.[15,17-20] Previously reported increases in peripheral blood eosinophil counts with lebrikizumab treatment are possibly due to decreased eosinophil trafficking from the blood to the airways as a result of reduced chemotaxis by blocking IL-13 activity.[15,20] In the TREBLE study, although eosinophil-associated AEs occurred only among lebrikizumab-treated patients, they were reported infrequently (n = 5 [3.2%]), all events were nonserious, and none were associated with clinical signs or symptoms, or resulted in dose reductions or treatment discontinuation.

The study protocol required twice daily TCS during the 2-week run-in period, and patients were only eligible for randomization if they manifested sufficient AD severity after this run-in. Although patients included in this study had a history of inadequate control by TCS, this TCS run-in nonetheless led to disease improvement, with lower baseline AD severity scores, especially itch. Although there is rationale for such a design, it does potentially leave less room for disease improvement than without a run-in period.

During the treatment period, patients continued twice-daily application of TCS, with daily e-Diary reminders, achieving an 88% compliance rate. TCS application might explain the substantial response observed in placebo and could also have attenuated placebo-corrected efficacy. Prolonged and frequent TCS use has been shown to result in progressive improvements in AD, but most guidelines suggest limiting daily use to avoid AEs.[23-25] However, while daily (not chronic) TCS use is typically recommended for acute lesions,[5] this proof-of-concept study sought to understand the potential efficacy of lebrikizumab in addition to continuous TCS and not to assess TCS-sparing. The chosen regimen is consistent with TCS labeling and was used because of regulatory concerns of off-label usage at a lower frequency than mandated by product labeling. It was also recognized that alternate designs could have led to substantial patient dropout and imputed patient failure within the control arm. Indeed, studies of biologic therapies in a monotherapy setting have led to dropout/imputed patient failure rates of ~50% within the control arm[13]; in contrast, the dropout rate of the placebo arm in this study was 13%.

Nonetheless, despite the relatively high efficacy of prolonged and frequent TCS use, there were still significant improvements, particularly in AD signs (EASI) and global scores (SCORAD) after addition of lebrikizumab.

Dupilumab, an IL-4Rα monoclonal antibody, demonstrated efficacy in patients with moderate-to-severe AD and has been recently approved for use in AD patients. IL-4Rα is a receptor subunit for both IL-4 and IL-13 signaling. Studies of dupilumab in AD patients provide insight into the potential of IL-13 blockade to treat AD, with the caveat that the relative importance of IL-4 compared with IL-13 in AD has not been established. Both IL-13 and IL-4 share overlapping biology and effector functions.[26,27] Given such high overlap in biology, blockade of IL-13 alone could potentially provide comparable improvements in AD to blockade of IL-13 and IL-4 in combination, with a more specific targeted action.

Targeting a soluble cytokine such as IL-13 might also offer the advantage of a linear pharmacokinetic profile, with resulting improvements in sustained target coverage and dosing frequency. This linear pharmacokinetic profile combined with the long half-life of lebrikizumab (19-22 days), in part, explains the ability to dose lebrikizumab every 4 weeks and might allow for less frequent dosing during maintenance. Indeed, the fact that single-dose groups showed improving placebo-corrected efficacy through week 8 suggests the potential for such a dosing regimen. In contrast, receptor targeting is associated with target-mediated drug clearance, which might lead to rapid declines in concentration after drug discontinuation or interruption, as with dupilumab, which is dosed every 2 weeks.[28]

The results of this proof-of-concept study suggest that IL-13–mediated signaling pathways play an important role in the pathogenesis of AD, and the blockade of this cytokine could lead to significant clinical benefit. Patients with moderate-to-severe AD showed improvements with lebrikizumab treatment, even with single doses and twice daily TCS use. However, the twice-daily use of TCS before and during this trial in all study groups impaired the ability to fully assess the efficacy of lebrikizumab in AD, and monotherapy studies may be needed to assess the efficacy of lebrikizumab. The dose-response relationships and kinetics of response observed in this study suggest that future studies of longer duration with loading, higher and potentially less frequent dosing, and a larger population on different (or without) background regimens will help clarify the role of targeting IL-13 with lebrikizumab in AD.

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SUPPLEMENTARY APPENDIX
SUPPLEMENTARY METHODS

Study design

This study included a 2-week topical corticosteroid (TCS) run-in period prior to the 12-week treatment period, with the goal of standardizing the background therapy before randomization and demonstrating failure to respond to TCS alone. To assess TCS adherence, patients were required to record medication use in e-Diary devices.

The study was undertaken in accordance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki. All study documents and procedures were approved by the appropriate institutional review boards and ethics committees at each study site, and each patient provided written informed consent before study participation. An internal monitoring committee was incorporated to monitor patient safety throughout the study.

Patients

Eligible patients had a diagnosis of moderate-to-severe AD as graded by the Rajka- Langeland criteria present for at least 1 year at screening.

In addition to those stated in the manuscript, key exclusion criteria included past and/or current use of any IL-13 or IL-4/IL-13 monoclonal antibody and a clinically significant abnormality on screening electrocardiogram or laboratory tests.

Randomization and masking

Three active doses were included to characterize both exposure—response relationships and dosing frequency requirements. A blocked randomization scheme stratified by region was used with a block size of 4. To maintain blinding, a placebo arm was included, and all patients were administered 2 prefilled syringes on day 1. Placebo patients received two 1-mL syringes filled with placebo, lebrikizumab 125 mg patients received one 1-mL syringe of lebrikizumab 125 mg/mL and one 1-mL syringe of placebo, and lebrikizumab 250 mg patients received two 1-mL syringes of lebrikizumab 125 mg/mL. All randomized patients received a total of 4 subcutaneous injections: 2 on day 1, 1 on day 29, and 1 on day 57, ie, 3 doses of study drug (lebrikizumab or placebo) over the first 8 weeks of the 12-week blinded treatment period. Placebo was prepared with the same formulation as lebrikizumab without addition of the active agent, and both formulations were identical in appearance.

Procedures

Assessments occurred on weeks 1, 4, 6, 8, and 12 during the 12-week treatment period. Days 1, 29, and 57 (weeks 1, 4, and 8) were treatment days, during which assessments were carried out before study drug administration. The Dermatology Life Quality Index and Atopic Dermatitis Impact Questionnaire (ADIQ) were self-administered at the study site before other nonpatient-reported outcome assessments. A study completion visit was performed at the end of week 20. The use of TCS other than that provided was prohibited.

As anaphylaxis, anaphylactoid, and hypersensitivity reactions are considered a potential risk with all biologic medications, all potential cases were identified and sent for adjudication by an independent lebrikizumab Anaphylaxis Adjudication Committee.

Pharmacokinetics

Serum samples for analysis of lebrikizumab pharmacokinetics were obtained in all patients at day 1 (pre-dose) and at weeks 1, 4 (pre-dose), 6, 8 (pre-dose), 12, 16, and 20 for all dosing regimens. Serum lebrikizumab concentrations were summarized by treatment and visit by using descriptive statistics for the patients that received 1 of the lebrikizumab treatment regimens. The reported pharmacokinetic parameters included the week 1 C_{max}; C_{min} at weeks 4, 8, and 12; and the elimination half-life.

Outcomes

In addition to those stated in the manuscript, key secondary efficacy endpoints included the percent change from baseline in Eczema Area and Severity Index (EASI) score at week 12; percent change from baseline in SCORing Atopic Dermatitis (SCORAD) at week 12; percent change from baseline in total % body surface area (BSA) affected at week 12; percent change from baseline in itch as measured by SCORAD pruritus Visual Analog Scale (VAS) at week 12; and absolute and percent change in Dermatology Life Quality Index and ADIQ.

Other analyses included percent change in SCORAD, sleep loss VAS, as well as percentage of patients with an absolute change in pruritus VAS ≥ 3 from baseline, where the threshold of 3 was based on the minimum clinically important difference for that instrument.

The ADIQ is an atopic dermatitis (AD)—specific measure of health-related quality of life for use in patients aged ≥ 12 years, developed by Genentech/Roche following US Food and Drug Administration patient-reported outcome Guidance (2009).

Statistical analyses

Enrollment of 50 patients per treatment group was estimated to provide at least 90% power to detect a 40% difference in the proportion of patients with EASI-50 between each lebrikizumab group and the placebo group at week 12, under the assumption of a two-sided type I error rate of 0.05, a dropout rate of

20%, and an EASI-50 rate at week 12 in the placebo group of ~20%.

Statistical analyses of all endpoints related to a binary outcome used the same methodology as described for the primary endpoint. Point estimates of the proportions by treatment group, corresponding differences from placebo, and associated two-sided 95% confidence intervals (CIs) for differences in proportions were provided.

Change from baseline for continuous endpoints was analyzed by using a mixed-effects model for repeat measures, including fixed effects of baseline value, treatment group, visit, treatment by visit interaction, and geographic region; the variable patient was included in the model as random effects with unstructured covariance structure. Missing data were implicitly imputed by the model (assuming missing at random). The 95% CIs and two-sided *P* values were reported for all secondary efficacy endpoints. No adjustments for multiplicity were made. All analyses were performed using SAS. An internal monitoring committee was incorporated to monitor patient safety throughout the study.

SUPPLEMENTARY RESULTS

Trial patients

A total of 294 patients were assessed for eligibility; 82 were ineligible and 212 patients were randomized. Of the 212 patients randomized, 209 received study drug. Among enrolled and treated patients, the mean age (standard deviation) at baseline was 36.1 ± 12.6 years; 35% were women and 72% were white. Patients had on average 47% of their BSA affected, an average SCORAD of 59, and an EASI of 25. These baseline severity scores were already improved in comparison to screening due to the 2-week run-in period with twice-daily TCS application (Supplemental Table II). The most common reason for screen failure (26 of 82 [31.7%] screen-failed patients) was patients not meeting the inclusion criterion of EASI score ≥14 due to improvements in EASI score during the run-in period.

Efficacy during safety follow-up

Overall, exploratory analyses showed that the proportion of patients maintaining EASI-50 (90.5%), EASI-75 (75.0%), and IGA 0 or 1 (70.6%) responses with lebrikizumab 125 mg every 4 weeks from week 12 to week 20 followed a similar pattern to that observed at week 12 (Supplemental Table V). Dose-dependent responses were also observed for percent change from baseline pruritus VAS at week 20.

Pharmacokinetics

The mean pharmacokinetic parameters and respective standard deviations for each of the lebrikizumab dosing regimens are shown in Supplemental Table VI (available at http://www.jaad.org). As expected, the pharmacokinetics of lebrikizumab in AD patients were linear and dose-proportional over the dose range tested. The pharmacokinetics of lebrikizumab was also consistent with that of previous studies in adult asthma,[S1-S4] showing linear, dose-proportional characteristics with a half-life of 19-22 days.

Safety

The rate of injection-site reactions was low in both the lebrikizumab-treated and placebo groups (1.3% and 1.9%, respectively). Herpes infections occurred infrequently and only in lebrikizumab-treated patients (6 [3.8%]; herpes simplex in 4 [2.6%], and herpes zoster in 2 [1.3%]); all events were nonserious, mild in intensity, and resolved by the end of the study. There were no events of eczema herpeticum. Five (3.2%) lebrikizumab-treated patients reported eosinophil-associated adverse events (AEs; 3 events of eosinophilia and 2 events of eosinophil count increased); all events were nonserious and mild-to-moderate in intensity. There were no associated clinical symptoms noted with these 5 AEs. The maximum eosinophil count in these 5 patients ranged 1.0-3.2 × 10^9/L; of these, 3 were grade 2 eosinophilia (1501-5000 cell/mm^3). The increases observed were in line with what has been seen in previous lebrikizumab studies.[S2,S5] Given the previous imbalances reported in biologic trials in AD,[S6] we evaluated conjunctivitis. A total of 15 (9.6%) patients in the pooled lebrikizumab group and 4 patients (7.5%) in the placebo group had conjunctivitis as an AE; all events were nonserious, none led to treatment discontinuation, and there was not a dose-response relationship.

SUPPLEMENTAL REFERENCES

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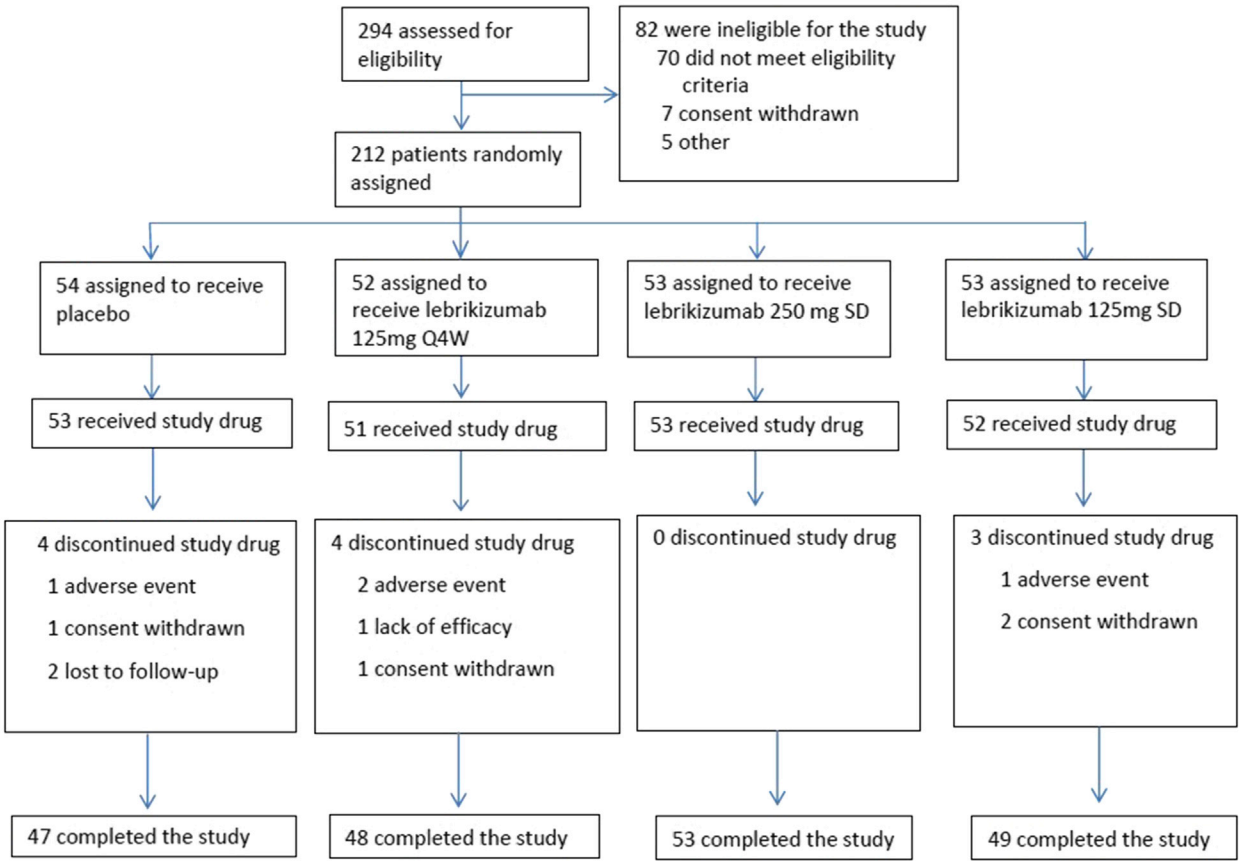

Supplemental Fig 1. Atopic dermatitis patient disposition for the TREBLE study. *Q4W*, Every 4 weeks; *SD*, single dose.

Supplemental Table I. Summary of primary and secondary efficacy outcomes for patients with atopic dermatitis taking lebrikizumab at week 12

Efficacy endpoint	Lebrikizumab 125 mg single dose, n = 52	Lebrikizumab 250 mg single dose, n = 53	Lebrikizumab 125 mg Q4W, n = 51	Placebo, n = 53
Primary endpoint				
EASI-50				
% patients	69.2	69.8	82.4	62.3
Δ (95% CI)	7.0 (−11.1 to 25.1)	7.5 (−10.4 to 25.5)	20.1 (3.4 to 36.8)	
P value	.48	.44	.026	
Secondary endpoints				
IGA 0 or 1				
% patients	21.2	28.3	33.3	18.9
Δ (95% CI)	2.3 (−13.0 to 17.6)	9.4 (−6.6 to 25.5)	14.5 (−2.2 to 31.2)	
P value	.77	.26	.098	
EASI-75				
% patients	38.5	49.1	54.9	34.0
Δ (95% CI)	4.5 (−13.9 to 22.9)	15.1 (−3.4 to 33.6)	20.9 (2.3 to 39.6)	
P value	.66	.12	.036	
EASI score, % change from baseline				
Adjusted mean (SE)	−58.5 (5.36)	−57.7 (5.26)	−70.5 (5.45)	−53.1 (5.38)
Δ (95% CI)	−5.3 (−20.3 to 9.7)	−4.6 (−19.4 to 10.3)	−17.4 (−32.5 to −2.2)	
P value	.48	.55	.025	
SCORAD-50				
% patients	34.6	47.2	51.0	26.4
Δ (95% CI)	8.2 (−9.4 to 25.8)	20.8 (2.8 to 38.7)	24.6 (6.4 to 42.7)	
P value	.38	.030	.012	
SCORAD, % change from baseline				
Adjusted mean (SE)	−38.7 (4.14)	−42.6 (4.07)	−53.5 (4.22)	−35.4 (4.16)
Δ (95% CI)	−3.3 (−14.9 to 8.3)	−7.2 (−18.7 to 4.3)	−18.0 (−29.7 to −6.4)	
P value	.57	.22	.0026	
Total % BSA affected, % change from baseline				
Adjusted mean (SE)	−45.2 (8.21)	−38.6 (8.07)	−57.7 (8.35)	−47.4 (8.24)
Δ (95% CI)	2.2 (−20.7 to 25.1)	8.8 (−13.9 to 31.6)	−10.3 (−33.4 to 12.9)	
P value	.85	.45	.38	
Pruritus (VAS), % change from baseline				
Adjusted mean (SE)	−34.9 (6.14)	−32.8 (5.95)	−40.7 (6.19)	−27.5 (6.12)
Δ (95% CI)	−7.4 (−24.5 to 9.7)	−5.3 (−22.1 to 11.6)	−13.2 (−30.3 to 4.0)	
P value	.40	.54	0.13	
Sleep loss (VAS), % change from baseline				
Adjusted mean (SE)	−53.1 (9.90)	−47.2 (9.83)	−53.6 (9.49)	−22.6 (9.70)
Δ (95% CI)	−30.6 (−57.9 to −3.2)	−24.6 (−51.8 to 2.6)	−31.0 (−57.8 to −4.2)	
P value	.029	.076	.023	
ADIQ, % change from baseline				
Adjusted mean (SE)	−33.2 (9.15)	−30.8 (8.99)	−54.3 (9.17)	−29.5 (9.13)
Δ (95% CI)	−3.7 (−29.2 to 21.8)	−1.3 (−26.6 to 24.0)	−24.8 (−50.3 to 0.7)	
P value	.77	.92	.057	
DLQI, % change from baseline				
Adjusted mean (SE)	−34.3 (6.93)	−40.7 (6.69)	−43.1 (7.02)	−33.6 (6.93)
Δ (95% CI)	−0.8 (−20.0 to 18.5)	−7.1 (−26.0 to 11.9)	−9.6 (−28.9 to 9.8)	
P value	.94	.46	.33	

ADIQ, Atopic Dermatitis Impact Questionnaire; *BSA*, body surface area; *CI*, confidence interval; *DLQI*, Dermatology Life Quality Index; *EASI-50*, 50% reduction in Eczema Area Severity Index; *EASI-75*, 75% reduction in Eczema Area Severity Index; *IGA*, Investigator Global Assessment; *Q4W*, every 4 weeks; *SCORAD*, SCORing Atopic Dermatitis; *SCORAD-50*, 50% reduction in SCORing Atopic Dermatitis; *SE*, standard error; *VAS*, Visual Analog Scale.

Supplemental Table II. Percent change in EASI, SCORAD, IGA, pruritus VAS, sleep loss VAS and percent BSA affected from screening to baseline (run-in) in atopic dermatitis patients taking lebrikizumab

Scoring system	Lebrikizumab 125 mg single dose, n = 52	Lebrikizumab 250 mg single dose, n = 53	Lebrikizumab 125 mg Q4W, n = 51	Placebo, n = 53	All patients, n = 209
Mean % change in EASI (SDv)	−14.3 (27.6)	−10.2 (29.2)	−9.1 (22.7)	−6.4 (32.2)	−10.0 (28.1)
Mean absolute change in IGA (SDv)	−0.21 (0.50)	−0.17 (0.51)	−0.14 (0.40)	−0.09 (0.45)	−0.15 (0.47)
Mean % change in SCORAD (SDv)	−12.2 (20.0)	−9.9 (14.7)	−7.7 (15.0)	−5.0 (20.3)	−8.7 (17.8)
Mean % change in % BSA affected (SDv)	−17.1 (26.7)	−4.3 (26.9)	−9.3 (27.0)	−6.2 (23.2)	−9.2 (26.3)
Mean % change in pruritus VAS (SDv)	−23.8 (29.6)	−15.5 (28.6)	−15.2 (39.4)	−12.8 (29.8)	−16.8 (32.1)
Mean % change in sleep loss VAS (SDv)	−29.0 (43.6)	−8.1 (81.8)	−12.9 (40.1)	−5.4 (57.2)	−13.9 (58.2)

BSA, Body surface area; *EASI*, Eczema Area Severity Index; *IGA*, Investigator Global Assessment; *Q4W*, every 4 weeks; *SCORAD*, SCORing Atopic Dermatitis; *SDv*, standard deviation; *VAS*, Visual Analog Scale.

Supplemental Table III. Atopic dermatitis. Overview of key safety information, weeks 0 to 20

Adverse events	Lebrikizumab 125 mg single dose, n = 54	Lebrikizumab 250 mg single dose, n = 52	Lebrikizumab 125 mg Q4W, n = 50	All lebrikizumab, n = 156	Placebo, n = 53
Patients with ≥1 AE, n (%)	38 (70)	39 (75)	27 (54)	104 (67)	35 (66)
AE leading to withdrawal from study drug, n (%)*	1 (2)	0 (0)	2 (4)	3 (2)	1 (2)
AE leading to dose modification/interruption, n (%)†	0 (0)	1 (2)	0 (0)	1 (1)	0 (0)
Patients with ≥1 SAE, n (%)	3 (6)	0 (0)	2 (4)	5 (3)	2 (4)
SAE leading to withdrawal from study drug, n (%)	0 (0)	0 (0)	1 (2) (Myopathy)	1 (1)	0 (0)
AEs of interest/events to be monitored, n (%)					
Adjudicated anaphylaxis per Sampson criteria‡	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections	24 (44)	20 (39)	12 (24)	56 (36)	24 (45)
Injection site reactions	0 (0)	0 (0)	2 (4)	2 (1)	1 (2)
Malignancies	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin infections, n (%)					
Patients with skin infection	6 (11)	5 (10)	3 (6)	14 (9)	9 (17)
Herpes infections					
Patients with ≥1 infection, n (%)	1 (2)	3 (6)	2 (4)	6 (4)	0 (0)
Total number of infections related to study drug§	0	0	0	0	0
Herpes simplex, n (%)	1 (2)	2 (4)	1 (2.0)	4 (3)	0 (0)
Herpes zoster, n (%)	0 (0)	1 (2)	1 (2.0)	2 (1)	0 (0)
Conjunctival infections, irritations, and inflammations					
Patients with ≥1 AE, n (%)	7 (13)	5 (10)	3 (6)	15 (10)	4 (8)
Total number of events	8	6	4	18	4
Conjunctivitis allergic, n (%)	4 (7)	2 (4)	2 (4)	8 (5)	0 (0)
Conjunctival hyperaemia, n (%)	0 (0)	1 (2)	0 (0)	1 (1)	0 (0)

AE, Adverse event; *Q4W*, every 4 weeks; *SAE*, serious adverse event.

*The following AEs led to withdrawal from study drug: skin infection in the 125 mg single dose group, anxiety and myopathy in 125 mg Q4W group, and atopic dermatitis in the placebo group.

†One (1%) patient in the 250 mg single dose lebrikizumab group experienced an AE (gastrointestinal viral infection) that led to dose interruption.

‡Members of the lebrikizumab Anaphylaxis Adjudication Committee reviewed blinded data to adjudicate cases as anaphylaxis per Sampson criteria.

§Infections related to study drug were investigator-assessed.

Supplemental Table IV. Principal investigator sites for TREBLE study

Site number	Investigator	Center
267701	*Simon, Dagmar	Inselspital Bern; Dermatologie, Freiburgstrasse, 3000, Bern, Switzerland
267730	*Remitz, Anita Reitamo, Sakari	Helsinki University Central Hospital; Skin & Allergy Hospital, Meilahdentie 2, PO Box 160, 00029, Helsinki, Finland
267731	*Snellman, Erna	Tampere University Hospital; Dermatology and Allergology, Teiskontie 35, Rakennusosa H, 33520, Tampere, Finland
267732	*Lammintausta, Kaija	Turku Central University Hospital; Dermatology and Allergology, Hämeentie 11 (Post Address PL52, 20521 Turku), 20250, Turku, Finland
268162	*de Bruin, Marjolein Bruijnzeel-Koomen, C.A.F.M.	Umc Utrecht; Dermatology, Heidelberglaan 100, Huispostnr.: F02.127, 3584 Cx, Utrecht, Netherlands
268163	*Schuttelaar, M.L.A.	University Medical Center Groningen; Department of Dermatology, Hanzeplein 1, De Brug, Room 2.084. Mailcode AB21 PO Box 30.001, 9700RB, Groningen, Netherlands
268592	*Spuls, Phyllis	Academisch Medisch Centrum Universiteit Amsterdam; Dermatology and VU University Medical Center, Meibergdreef 9, 1100 DD, Amsterdam, Netherlands
275003	*Solomon, James	Ameriderm Research, 725 West Granada Boulevard, Suite 44, Ormond Beach, FL, 32174, United States
275005	*Maari, Catherine Nigen, Simon	Innovaderm Research Inc., 1851 Sherbrooke St. East, Suite 502, L2K 4L5, Montreal, Quebec, Canada
275031	*Raman, Mani	The Centre for Dermatology, 312 Highway 7 East, L4B 1A5, Richmond Hill, Ontario, Canada
275032	*Papp, Kim	K. Papp Clinical Research Inc., 135 Union Street East, N2J 1C4, Waterloo, Ontario, Canada
275033	*Sadick, Neil	Sadick Research Group, 911 Park Avenue, Suite 1a, New York, NY, 10075, United States
275034	*Gooderham, Melinda	Dr. Melinda Gooderham Medicine Professional Corporation, 775 Monaghan Road South, K9J 5K2, Peterborough, Ontario, Canada
275035	*Davis, Steven	Dermatology Clinical Research Center of San Antonio, 7810 Louis Pasteur Drive, Suite 200, San Antonio, TX, 78229, United States
275085	*Dunnick, Cory Armstrong, April	University of Colorado; Anschutz Cancer Pavilion, 12801 E. 17th Ave., Mail Stop F703, Room 3232, Aurora, CO, 80045, United States
275088	*Ciliberto, Heather	University of Iowa Healthcare; Dermatology, 200 HAWKINS DRIVE, T307-GH, Iowa City, IA, 52242, United States
275093	*Toth, Darryl	Xlr8 Medical Research Inc., 2425 Tecumseh Road East, Suite 210, N8W 1E6, Windsor, Ontario, Canada
275094	*Pariser, David	Virginia Clinical Research Inc., 6160 Kempsville Circle, Suite 200a, Norfolk, VA, 23502, United States
275095	*Sofen, Howard	Dermatology Research Associate, 8930 S. Sepulveda Blvd., Suite 114, Los Angeles, CA, 90045, United States
275193	*Adams, Stewart	Institute for Skin Advancement, 4935 40th Avenue NW, Suite 206, Market Mall Professional Building, T3A 2N1, Calgary, Alberta, Canada
275251	*Silverberg, Jonathan	Northwestern University Feinberg School of Medicine, 710 North Lake Shore Drive; Abbott Hall, Room 1123, Chicago, IL, 60611, United States
275253	*Hebert, Adelaide	University of Texas Medical School-Houston, 6655 Travis, Suite 600, Houston, TX, 77030, United States
275371	*Simpson, Eric	Oregon Health & Science University; Department of Dermatology, 3303 SW Bond Ave., Mail Code: CH16D, Portland, OR, 97239-4501, United States
275372	*Murakawa, George	Somerset Skin Centre, 255 Kirts Blvd., Troy, MI, 48084, United States
275758	*Foley, Peter	Skin & Cancer Foundation, Level 1 80 Drummond St, 3053, Carlton, Victoria, Australia
275792	*Sheu, Hamm-Ming	National Cheng-Kung University Hospital; Department of Dermatology, 138 Sheng-Li Road, 70403, Tainan, Taiwan
275793	*Chu, Chia-Yu	National Taiwan University Hospital; Department of Dermatology, 2F, No.1, Changde St, Zhongzheng District, 10048, Taipei, Taiwan

Continued

Supplemental Table IV. Cont'd

Site number	Investigator	Center
275794	*Lee, Chih-Hung	Chang Gung Medical Foundation; Kaohsiung Branch; Department of Dermatology, No.123, Dapi Road, Niaosng District, 83301, Kaohsiung, Taiwan
276106	*Varigos, George	Royal Melbourne Hospital; Dermatology Department, Grattan St., Level 2 East Main Block Room E200, 3050, Parkville, Victoria, Australia
276128	*Bzdulska-Doskocz, Beata	ALERGO-MED Specjalistyczna Przychodnia Lekarska Sp. Z O. O, Ul. PCK 26, 33-100, Tarnow, Poland
276143	*Gebauer, Kurt	Fremantle Dermatology, 229 High Street, 6160, Fremantle, Western Australia, Australia
276145	*Shumack, Stephen	St George Dermatology and Skin Cancer Centre, Level 3, 22 Belgrave Street, 2217, Kogarah, New South Wales, Australia
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Continued

Supplemental Table IV. Cont'd

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*Indicates the current Principal Investigator. The names of previous Principal Investigators, if any, are also listed.

Supplemental Table V. Key efficacy outcomes of atopic dermatitis patients taking lebrikizumab at week 20

Outcomes	Lebrikizumab 125 mg single dose	Lebrikizumab 250 mg single dose	Lebrikizumab 125 mg Q4W	Placebo
Patients maintaining EASI-50 response from week 12 to week 20				
N (%)	29/36 (80.6)	29/37 (78.4)	38/42 (90.5)	24/33 (72.7)
Placebo-corrected differences (SE)	7.8	5.7	17.8	
P value	.39	.58	.047	
Patients maintaining EASI-75 response from week 12 to week 20				
N (%)	9/20 (45.0)	16/26 (61.5)	21/28 (75.0)	12/18 (66.7)
Placebo-corrected differences (SE)	−21.7	−5.1	8.3	
P value	.20	.81	.54	
Patients maintaining IGA 0 or 1 response from week 12 to week 20				
N (%)	6/11 (54.5)	9/15 (60.0)	12/17 (70.6)	6/10 (60)
Placebo-corrected differences (SE)	−5.5	0	10.6	
P value	.97	.94	.58	
Patients maintaining SCORAD-50 response from week 12 to week 20				
N (%)	11/18 (61.1)	16/25 (64.0)	13/26 (50.0)	11/14 (78.6)
Placebo-corrected differences (SE)	−17.5	−14.6	−28.6	
P value	.34	.49	.13	
Percent change from baseline in EASI				
Adjusted mean % change (SE)	−62.1 (5.43)	−55.9 (5.28)	−71.1 (5.50)	−54.1 (5.49)
Placebo-corrected differences (95% CI)	−8.1 (−23.3 to 7.1)	−1.9 (−16.9 to 13.2)	−17.1 (−32.4 to −1.7)	
P value	.30	.81	.03	
Percent change from baseline in the % BSA affected				
Adjusted mean % change (SE)	−53.6 (6.10)	−46.4 (5.96)	−63.8 (6.19)	−52.0 (6.16)
Placebo-corrected differences (95% CI)	−1.6 (−18.7 to 15.5)	5.6 (−11.4 to 22.5)	−11.8 (−29.0 to 5.5)	
P value	.85	.52	.18	
Percent change from baseline pruritus VAS				
Adjusted mean % change (SE)	−27.6 (7.64)	−30.3 (7.36)	−35.2 (7.68)	−21.5 (7.66)
Placebo-corrected differences (95% CI)	−6.1 (−27.5 to 15.2)	−8.8 (−29.7 to 12.2)	−13.8 (−35.2 to 7.6)	
P value	.57	.41	.21	

BSA, Body surface area; *CI*, confidence interval; *EASI-50*, 50% reduction in Eczema Area Severity Index; *EASI-75*, 75% reduction in Eczema Area Severity Index; *IGA*, Investigator Global Assessment; *Q4W*, every 4 weeks; *SCORAD-50*, 50% reduction in SCORing Atopic Dermatitis; *SE*, standard error; *VAS*, Visual Analog Scale.

Supplemental Table VI. Mean lebrikizumab pharmacokinetic parameters after single or multiple dose subcutaneous administration in atopic dermatitis patients

Pharmacokinetic parameter	Lebrikizumab 125 mg single dose	Lebrikizumab 250 mg single dose	Lebrikizumab 125 mg Q4W
Mean $C_{max,\ wk1}$ μg/mL (SDv)	17.0 (5.22)	35.6 (10.8)	16.1 (5.19)
Mean $C_{min,\ wk4}$ μg/mL (SDv)	10.2 (3.00)	21.4 (6.87)	9.15 (2.99)
Mean $C_{min,\ wk8}$ μg/mL (SDv)	4.59 (2.12)	9.53 (3.53)	13.6 (5.34)
Mean $C_{min,\ wk12}$ μg/mL (SDv)	2.28 (1.72)	3.77 (2.01)	14.4 (5.69)
$t_{1/2}$, day	18.5 (5.06)	22.2 (6.18)	20.9 (4.17)

$C_{max,\ wk1}$, Maximum lebrikizumab concentration at week 1; $C_{min,\ wk4}$, observed minimum concentration at week 4; $C_{min,\ wk8}$, observed minimum concentration at week 8; $C_{min,\ wk12}$, observed minimum concentration at week 12; *Q4W*, every 4 weeks; *SDv*, standard deviation; $t_{1/2}$, elimination half-life.